GROWTH HORMONE AND SEROTONIN ANTAGONIST

To the Editor: In their recent paper Bivens, Lebovitz, and Feldman[1] presented data showing attenuation of the response of serum growth hormone (GH) to insulin stimulation in normal subjects treated with cyproheptadine or methysergide. Because an increase in hypothalamic serotonin content has been found in laboratory animals during induced hypoglycemia, and because intraventricular administration of serotonin stimulates GH secretion in the rat, the authors concluded from their experiment that these two serotonin antagonists probably interfered with hypothalamic serotonin stimulation of GH secretion. Most pharmacologic studies, however, would argue otherwise.

The antiserotonin activity of cyproheptadine and methysergide appears to be confined to peripheral receptor-site blockade of this monoamine.[2] Neither drug changes central-nervous-system serotonin concentration nor has central antiserotonin action at doses appreciably below the LD_{50} for laboratory animals.[3,4] Indeed, because it is strongly hydrophilic, methysergide is poorly transported across the blood-brain barrier, if at all.[5] It therefore seems unlikely that these agents act centrally to modify pituitary secretion of GH. How they act remains unknown. Possibly, they reduce serum GH by affecting the hormone's peripheral metabolism.

It is sometimes as easy to tell which comes first in the serotonin-GH relation as it is in the chicken-egg one. For example, in animals treated with GH there is increased weight and granularity of enterochromaffin cells,[6] and increased urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA),[7] whereas opposite effects on the enterochromaffin cells are noted after hypophysectomy.[8] Thus, an increase in serum GH may stimulate serotonin synthesis and turnover in peripheral serotonin-rich pools. We have some data to suggest that serum GH affects serum serotonin concentration in man. Five acromegalic patients had a mean fasting serum GH of 27.90 ± 6.31 μg per milliliter and elevated mean fasting serum serotonin level of 0.91 ± 0.31 μg per milliliter. Within three months after trans-sphenoidal resection of the pituitary tumor in this group, mean serum GH level fallen to 7.62 ± 2.33, and mean serum serotonin to 0.57 ± 0.10 μg per milliliter. The serum serotonin:5-HIAA ratio was [illegible] high (5.8:1) before and was normal (2.1:1) after operation—a statistically significant decline (chi-square = 17.02, $p < 0.01$). Thus, peripheral blood levels of serotonin appeared to follow changes in serum GH produced by pituitary-adenoma resection. Whether the reverse effects (changes in peripheral serotonin concentration, or in the ability of serotonin to attach to appropriate peripheral receptor sites) induce changes in serum GH are unknown to us.

Though we question the presumed mechanism, we applaud the discovery of attenuation of serum GH response to hypoglycemia by serotonin antagonists. These agents may be useful, possibly when combined with compounds having central antiadrenergic activity,[9] in experimental drug therapy of acromegaly and gigantism.[10]

WALTER B. ESSMAN, M.D., PH.D.
LAWRENCE SHERMAN, M.D.
HOWARD D. KOLODNY, M.D.

N. Engl. J. Med. 289: 870-871, 1973